Case Reports

The Efficacy of Pl^{A1}-Negative Platelet Transfusion Therapy in Posttransfusion Purpura

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POSTTRANSFUSION PURPURA is an uncommon, immune-mediated acute thrombocytopenia that occurs one to two weeks after a blood transfusion in patients with no previous evidence of alloimmunity or autoimmunity against platelets.[1-4] This syndrome generally occurs postoperatively in elderly patients and produces a mortality rate of 10% to 15%. Most information regarding treatment is based on individual case reports; therefore, no definitive standard therapy can be outlined. Although the pathogenesis of this disorder is almost always related to the presence of the antibody against the platelet-specific Pl^{A1} antigen,[1-5] the use of a Pl^{A1}-negative platelet transfusion is generally not considered effective.[2,3,6-8] We know of only four cases, however, in which Pl^{A1}-negative platelet transfusion therapy has been attempted, and the results have been conflicting.[2,6-8] Herein we describe an effective treatment of posttransfusion purpura with the use of Pl^{A1}-negative platelet transfusion and discuss factors that may affect the success of this therapy.

Report of a Case

The patient, a 69-year-old woman, was admitted to hospital for a coronary artery bypass graft reoperation. The medical history was notable for three uncomplicated pregnancies and a coronary artery bypass graft six years earlier requiring multiple transfusions. Her medications included nifedipine, propranolol hydrochloride, diazepam, quinidine and nitroglycerin. No abnormalities were found on physical examination. The findings of a laboratory evaluation, which included complete blood counts, were within normal limits.

Because of excessive bleeding from the adhesions and scar tissue in the operative site, she received nine units of whole blood, four units of fresh frozen plasma and six units of random donor platelets. During the operation we noted a transient thrombocytopenia typical of that occurring in patients with extracorporeal circulation and hemodilution, which resolved completely five days later. The surgical procedure was complicated by an embolic cerebrovascular accident (CVA) with vocal cord paralysis. Subsequent difficulty mobilizing pulmonary secretions led to a tracheostomy on the fifth postoperative day, at which time two units of packed red cells were transfused. Although clinically stable, she required two units of Jk^a-negative packed red cells three days later because of an asymptomatic delayed transfusion reaction caused by an anti-Jk^a antibody. Over the next two to four days, six units of fresh frozen plasma, nine units of random donor platelets and two units of packed red cells were administered because of continued oozing from the tracheostomy site. The platelet estimate remained unchanged (median 75,000 per μl) after the random donor platelet transfusion. The prothrombin time, partial thromboplastin time and levels of fibrinogen and fibrin-split products were within normal limits. The platelet count was estimated to be decreased.

ABBREVIATIONS USED IN TEXT
CVA = cerebrovascular accident
HLA = human leukocyte antigen

Several days later spontaneous petechiae developed, and the presence of thrombocytopenia was confirmed (Figure 1). At this time platelet antibody and antigen testing showed that the patient's platelets were Pl^{A1}-negative and her serum contained an anti-Pl^{A1} antibody; no other platelet, lymphocyte, granulocyte or drug antibodies were detected. Earlier blood specimens were subsequently retrieved for testing, and the laboratory data from these tests are shown in Figure 1 and described in the Results section. Because the patient was elderly, recovering from an open-heart procedure complicated by a CVA and bleeding from mucocutaneous sites of trauma, such as the tracheostomy site, one unit of Pl^{A1}-negative platelets from a single apheresis donor was transfused four days later. The one-hour posttransfusion platelet increment was greater than 80,000 per μl, and no further clinical bleeding occurred. The patient's platelet count decreased

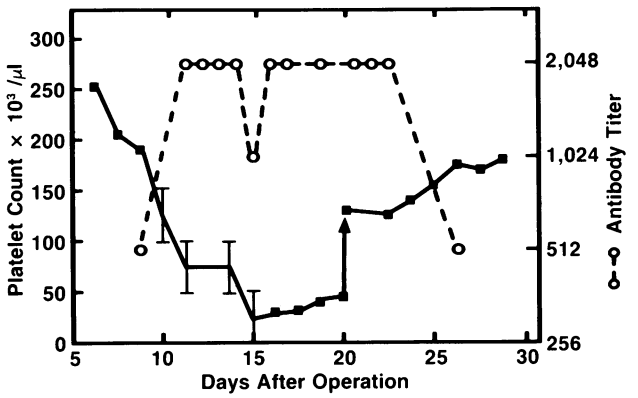

Figure 1.—The graph depicts the clinical course of the patient with posttransfusion purpura. Note the excellent response to Pl^{A1}-negative platelet transfusion despite the presence of a high-titered (2,048) anti-Pl^{A1}. Anti-Pl^{A1} was first detected on the 8th postoperative day. ↑ = One hour posttransfusion platelet count after a transfusion of Pl^{A1}-negative single-donor-platelet apheresis equivalent to 6 to 8 units of platelet concentrate. I = Exact platelet count not available; this is a semiquantitative estimate from the peripheral blood smear. The platelet count curve is drawn through the median of the range for which these estimates have previously been standardized.

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slightly over the next two days, but then steadily increased and remained normal during the next six weeks of observation.

Materials and Methods

Pools of serum from male AB donors were used as negative controls. Serum specimens were taken from the patient at the times noted, and the serum was stored at −76°C. Typing serum was from the reagent collection of one of us (F.C.G.).

As we reported previously,[9,10] the C-FDA and KC-FDA thrombocytotoxicity assays were done to test for PI^{A1} antigen and antibody and other antiplatelet alloantibodies or drug-related antibodies. One μl of platelets labeled with the vital dye carboxyfluorescein diacetate was dispensed into standard tissue-typing trays preloaded with relevant sera. After the first incubation at 37°C for 30 minutes, the platelets were washed three times (in the trays) with a phosphate-buffered saline solution. One μl of an appropriate dilution of goat anti-human light chain (κ) was added to each well and incubated for two minutes at room temperature. Complement (fresh frozen rabbit serum) was then added, and after it had incubated for 90 minutes at room temperature, test results were read under low-power fluorescence microscopy with appropriate filters for fluorescein excitation. Wells were considered positive if their visibility was at least 50% less than that of the AB control well.

The procedure described above was also used to test for drug antibodies, except that 1 μl of 1 mg per ml of suspension of the appropriate drug was added to the relevant sera in the wells. If cell lysis occurs in wells with added drug but not in control wells, this indicates the presence of drug-related antibodies.

Fluorochromasia lymphocytotoxicity testing was also done, as reported previously by us and others.[9,11]

Erythrocyte serologic techniques followed the standard blood bank procedures of using a solution of low ionic strength or routine saline, albumin or enzyme techniques.[12]

Results

When tested for antibody specificity, serum specimens collected on several postoperative days, as indicated in Figure 1, were strongly reactive with 20/20 PI^{A1}-positive panel platelets and nonreactive with 9/9 PI^{A1}-negative panel platelets. Anti-PI^{A1} titers are also shown in Figure 1 and range from 512 to 2,048.

Tests for thrombocytotoxic antiquinidine antibodies were also negative. No anti-human leukocyte antigen (HLA) antibodies were detected when serum (from postoperative days 10, 15 and 22) was screened against a panel of 60 HLA-typed lymphocytes. The patient's HLA type was A1, A3, B8, B35, Bw6. Crossmatches of her serum with the PI^{A1}-negative platelets of her apheresis donor were negative.

As seen in Figure 1, transfusion of PI^{A1}-negative platelets produced a therapeutic posttransfusion platelet increment (80,000 per μl at one hour) even at a time when the patient's anti-PI^{A1} antibody titer was 2,048; this increment was associated with a definite clinical response of hemostasis with no adverse reactions.

Discussion

Posttransfusion purpura is a self-limited disorder with a median duration of thrombocytopenia of about three weeks when untreated.[1-4] It is, however, potentially lethal, with an estimated mortality rate of 10% to 15%, and can cause significant morbidity, making the initial choice of therapy critical. Although most cases are related to alloimmunization and alloantibody formation against the high-frequency, platelet-specific antigen PI^{A1}, the role of PI^{A1}-negative platelet transfusions is uncertain.[2,3,6-8,13] In neonatal isoimmune thrombocytopenia caused by an anti-PI^{A1} antibody, PI^{A1}-negative—such as maternal—platelet transfusion is uniformly effective.[4]

The present case conforms to the typical clinical pattern of posttransfusion purpura: an older woman belonging to the 2% to 3% of the PI^{A1}-negative population, who was probably sensitized to the PI^{A1}-antigen during her pregnancies or previous transfusions and in whom thrombocytopenia developed one to two weeks after a recent transfusion. She had a definite therapeutic response to the PI^{A1}-negative platelet transfusion as shown by the greater than 80,000 per μl posttransfusion increase in platelet count within an hour and cessation of mucocutaneous bleeding. Furthermore, her response occurred only one week after the onset of thrombocytopenia and in the presence of a high titer of circulating anti-PI^{A1} antibodies (Figure 1). Although her counts appeared to be increasing gradually, it is evident that her recovery was greatly accelerated by the PI^{A1}-negative platelet transfusion.

Including the present case, the use of PI^{A1}-negative platelet transfusion has been reported in only five patients,[2,6-8] two of whom had definite responses indicated by an increased platelet count or cessation of bleeding, or both (this case and that reported by Le Roux and co-workers).[7] Based on the two responding patients, it seems reasonable to use PI^{A1}-negative platelet transfusion in patients like these who had no HLA antibodies or febrile transfusion reactions (which may indicate the presence of leukocyte antibodies).[14-17]

Although the number of reported cases is small, a response rate of 40% (two of five) at the very least is promising. The inefficacy of PI^{A1}-negative platelet transfusion in the three nonresponding patients may reflect factors such as an unrecognized heterogeneity of PI^{A1} antigen (or antibody) or coincident antibodies to non-PI^{A1} and possibly to nonplatelet antigens. Because PI^{A1}-negative platelet transfusion has the potential of giving immediate benefit and is relatively safe, a therapeutic trial of this therapy in patients with posttransfusion purpura is justified. Further studies are needed to ascertain which patients present the best profile for receiving PI^{A1}-negative platelet transfusion therapy.

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Vitamin A Intoxication Presenting With Ascites and a Normal Vitamin A Level

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VITAMIN A SUPPLEMENTATION by health practitioners and the nonmedical public is becoming increasingly common. Unfortunately, the toxic risks of taking vitamin A are often not appreciated. We report here a case of vitamin A intoxication that was unusual in presentation, with ascites and a normal serum vitamin A level on initial determination.

Report of a Case

The patient, a 3-year-old girl with failure to thrive, was seen after two months of lower extremity pain, periods of refusing to walk, irritability, lethargy, bleeding gums, peeling erythematous skin, pruritus and a protuberant abdomen. On physical examination her vital signs were normal, she was thin and irritable and had mild abdominal distension. Her weight was 11.0 kg (24 lb) and height 84 cm (33 in), both below the fifth percentile. Her head circumference was at the tenth percentile. She showed no abdominal organomegaly nor a fluid wave, and there were no joint abnormalities. The skin was somewhat dry, and results of the rest of the examination were normal. All of the following studies elicited normal values: a complete blood count, platelets, erythrocyte sedimentation rate (ESR), serum alanine aminotransferase (ALT [formerly SGPT]), calcium, uric acid and electrolytes. A urinalysis, urine culture, sweat chloride test and Epstein-Barr virus and cytomegalovirus titers were also negative. A plain film of the abdomen was normal.

After two weeks of observation, she was admitted to hospital because of ascites with respiratory distress. Her weight was 12.6 kg (27.8 lb), her temperature 38.0°C (100.4°F), respiratory rate 30 per minute, heart rate 120 beats per minute and blood pressure 110/60 mm of mercury. New physical findings included a greatly distended and tense abdomen without liver or spleen enlargement, a prominent venous pattern on the abdomen, decreased breath sounds and rales in the right lower lung field, a dry and erythematous skin and brittle hair with alopecia. The extremities were normal with a full range of motion and without pain. Except for irritability, no abnormalities were found on neurologic examination. The fundi were normal.

ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
ESR = erythrocyte sedimentation rate
RBP = retinol-binding protein

A paracentesis showed clear and yellow fluid, a leukocyte count of 80 per μl with no polymorphonuclear neutrophils, erythrocytes 510 per μl, glucose 9.0 mg per dl, protein 3.4 mg per dl, albumin 2.3 mg per dl, amylase 14 IU per liter and lactic dehydrogenase 221 IU per liter. The fluid specimen was negative for bacteria, acid-fast bacilli and fungi, and cytologic tests were negative. Blood studies showed the following values: aspartate aminotransferase (formerly SGOT) 80, ALT 31 and alkaline phosphatase 153 IU per liter; total protein 5.2 mg per dl, and albumin 3.4 mg per dl. Results of all of the following studies were normal: prothrombin time; partial thromboplastin time; serum levels of electrolytes, creatinine, calcium, phosphate, uric acid, and amylase; ESR; fluorescent antinuclear antibody, C3 and C4 levels; DNA binding, quantitative immunoglobulins, and a bone marrow biopsy. Tests for tumor markers were negative.

A chest x-ray film showed a normal-sized heart and a right pleural effusion. An abdominal ultrasonogram and a body computed tomographic scan showed massive ascites, a normal liver and spleen, a soft tissue mass in the region of the head of the pancreas and a small calcification in the upper pole of the right kidney. Bone and liver-spleen scans were normal. A lymphangiogram and a nuclear scan study using technetium Tc 99m-labeled antimony showed no lymphatic leakage into the peritoneal cavity.

Upon further discussion, the parents reported that a chiropractor had prescribed vitamin A supplementation seven months earlier because of poor weight gain and eczema. The vitamin A was given at a dose of 100,000 IU per day for one week, then 50,000 IU per day for the following six months, ending one month before her presentation. By history, no other vitamin supplementation had been given. The patient was evaluated for vitamin A toxicity. Long-bone radiographs were normal. Serum vitamin A and carotene levels were 196 IU per dl (normal 65 to 275) and 17 μg per dl (normal 50 to 300), respectively.

An exploratory laparotomy was done because of a suspected intra-abdominal tumor. It showed normal liver, spleen, kidneys, reproductive tract, pancreas, and lymph nodes. There was no inflammation of the serosal surface. A portal venogram showed a hepatic wedge pressure of 150 mm of water (upper limits of normal for adults) and no evidence of obstruction. A liver biopsy specimen showed mild patchy centrilobular sclerosis around the central vein, pericellular sclerosis surrounding individual hepatocytes, and focal prominence of Ito cells shown by fluorescence microscopy. There

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